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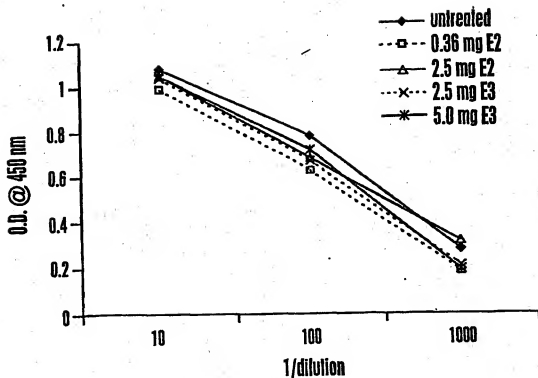


Figure 6

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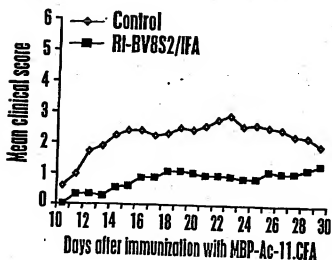


Figure 7A

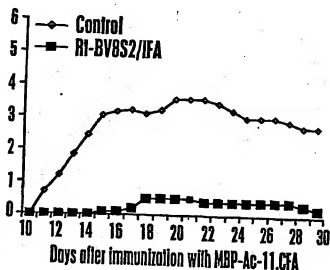


Figure 7B

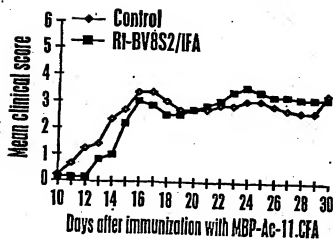


Figure 7C

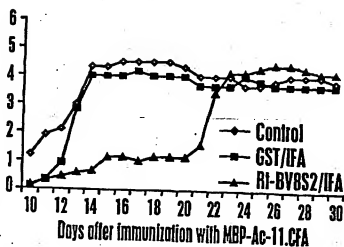


Figure 7D

SUBSTITUTE SHEET (RULE 26)

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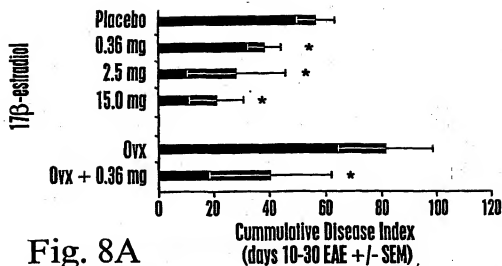


Fig. 8A

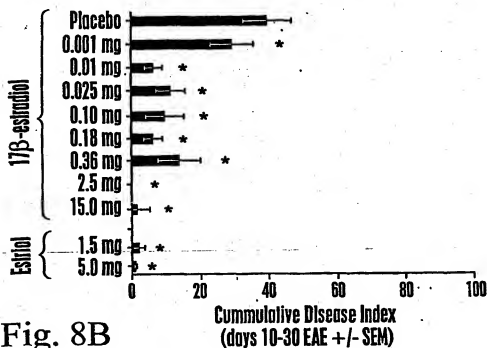


Fig. 8B

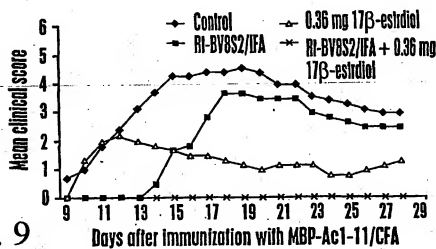
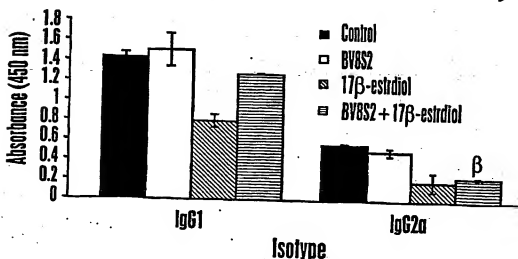
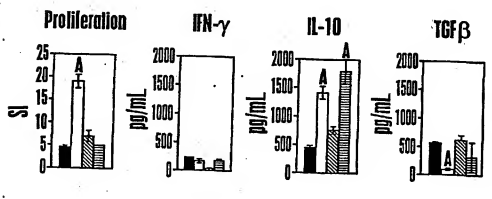
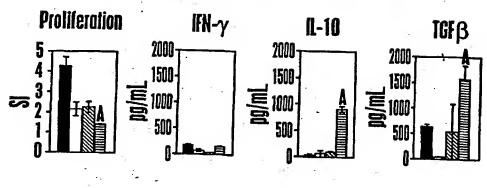
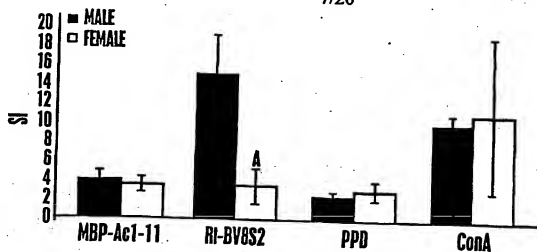


Fig. 9

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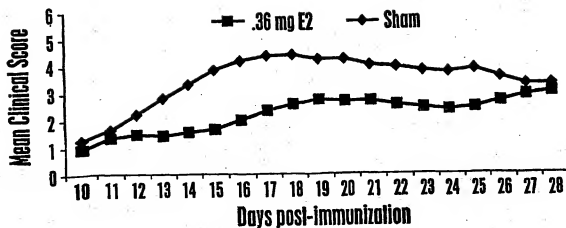


Figure 11A

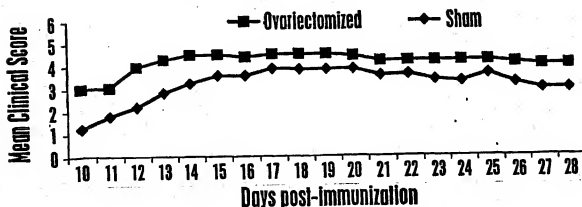


Figure 11B

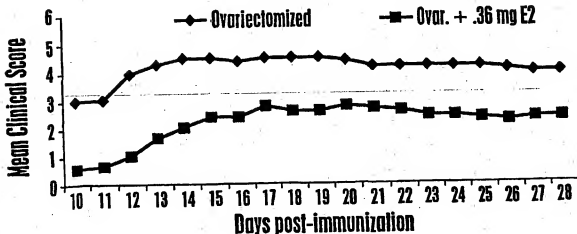


Figure 11C

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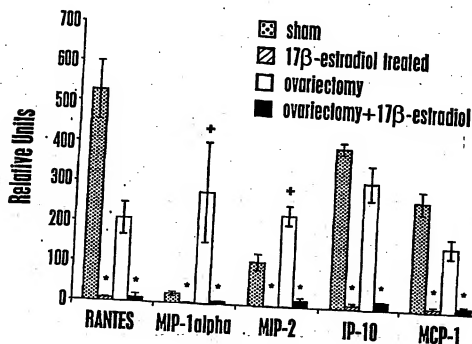


Fig. 12

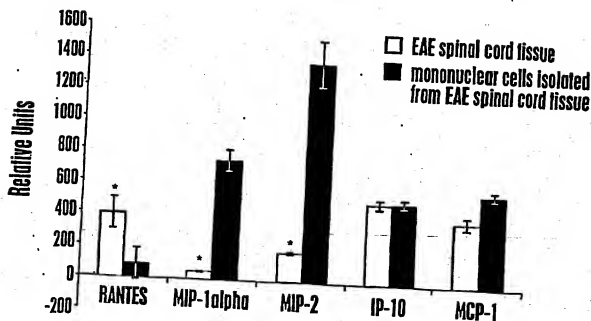


Fig. 13

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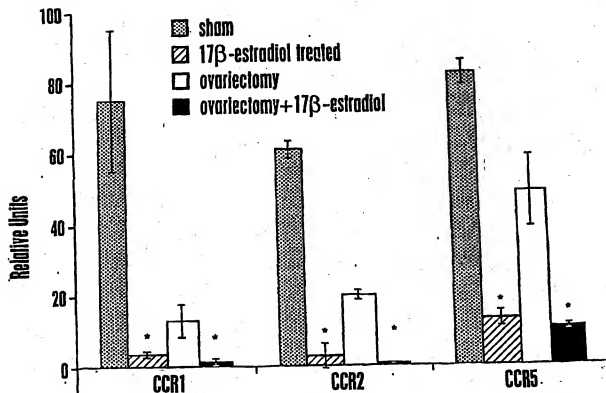


Figure 14.

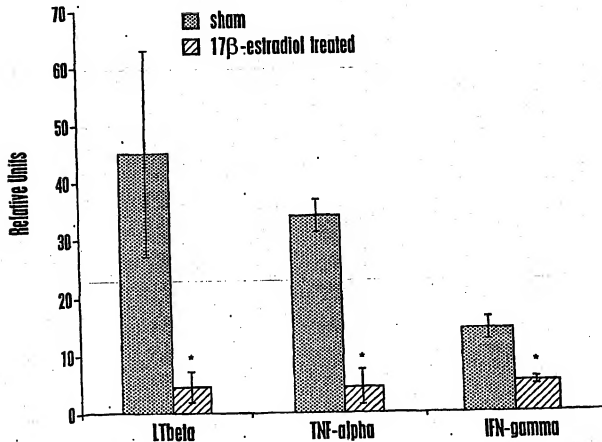


Figure 15

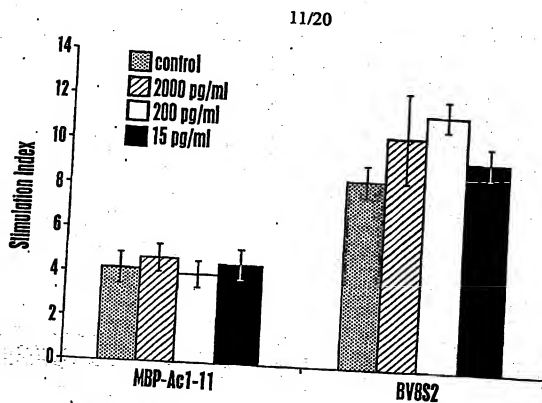


Figure 16A

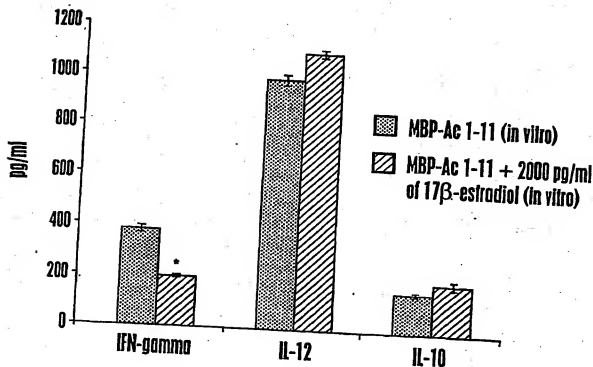


Figure 16B

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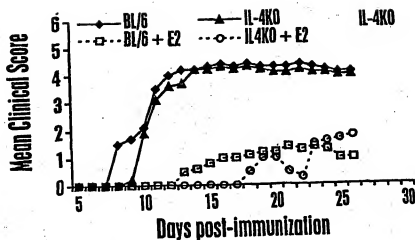


Fig. 17A

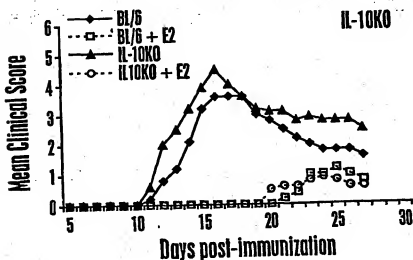


Fig. 17B

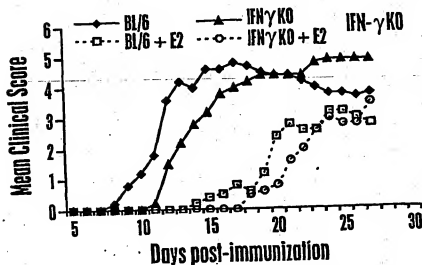


Fig. 17C

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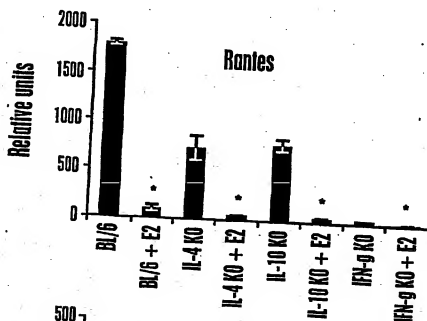


Fig. 18A

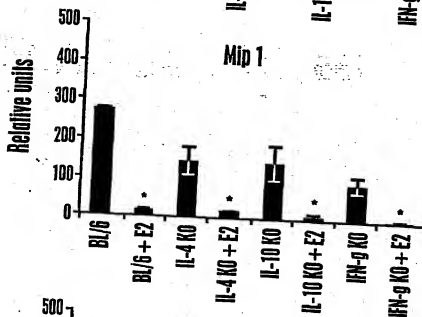


Fig. 18D

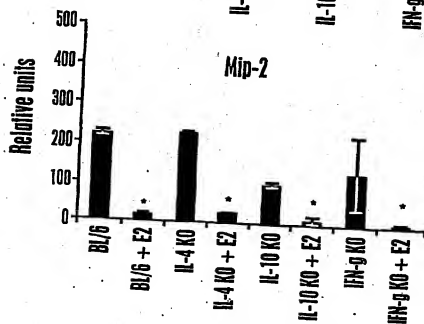


Fig. 18G

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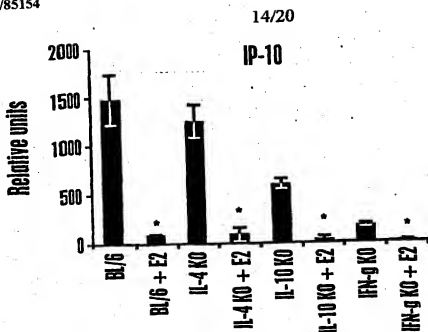


Fig. 18B

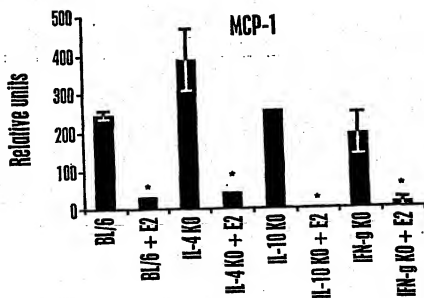


Fig. 18E

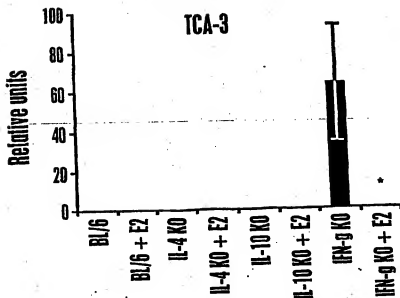


Fig. 18H

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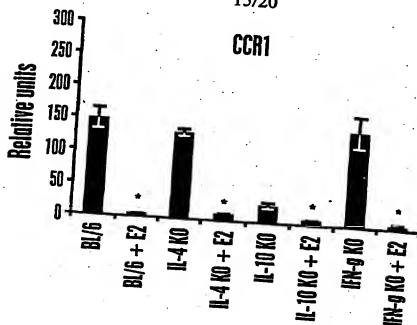


Fig. 18C

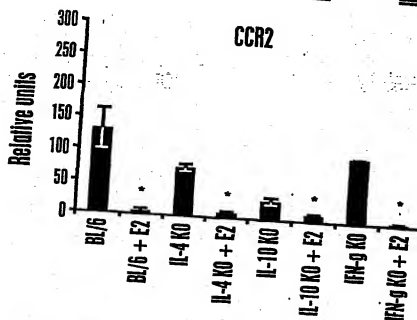


Fig. 18F

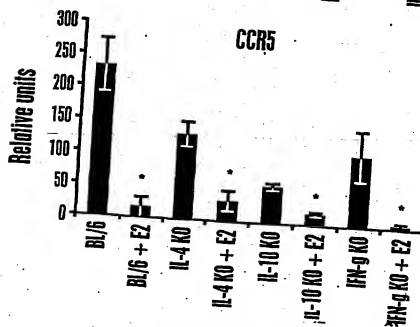


Fig. 18I

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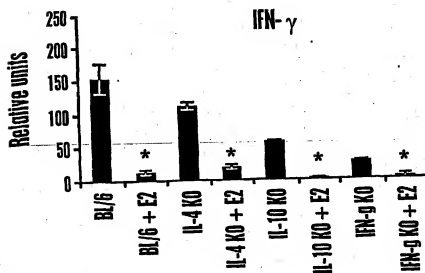
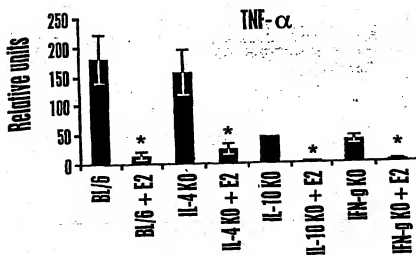
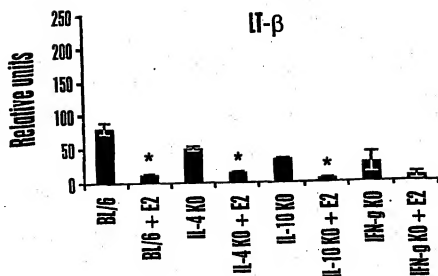


Figure 19A

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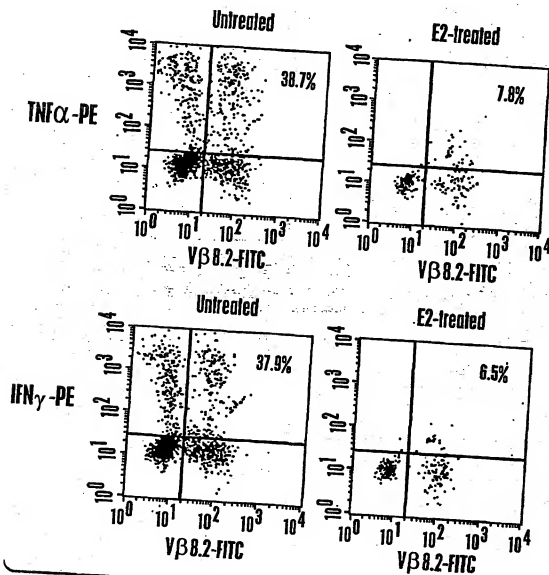


Figure 19B

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Figure 20A

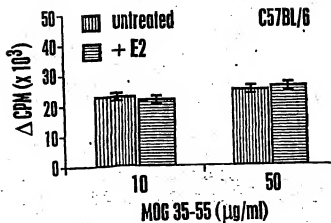


Figure 20B

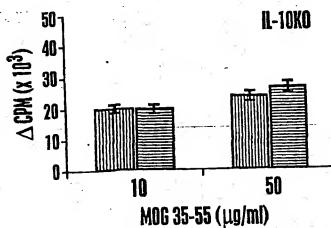
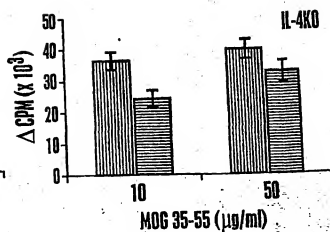


Figure 20C

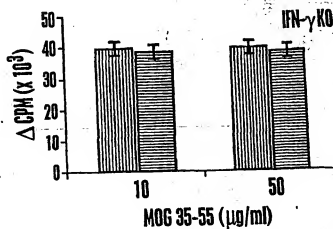


Figure 20D

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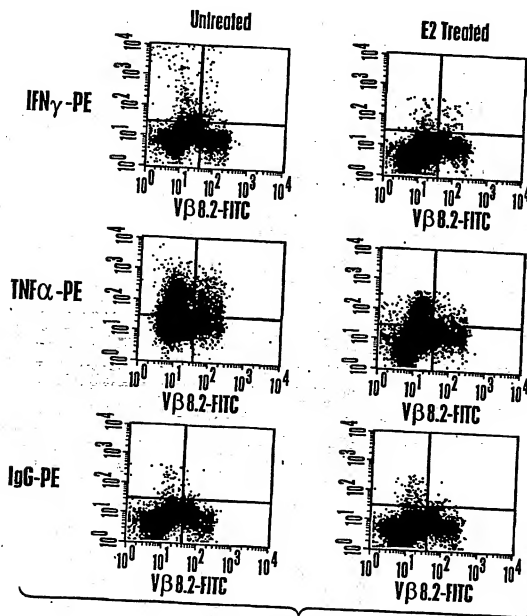


Figure 21A

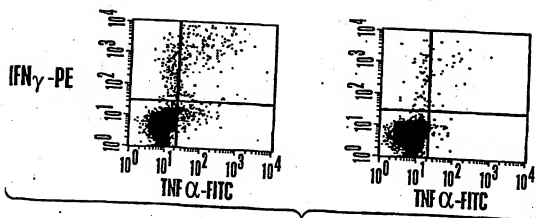


Figure 21B

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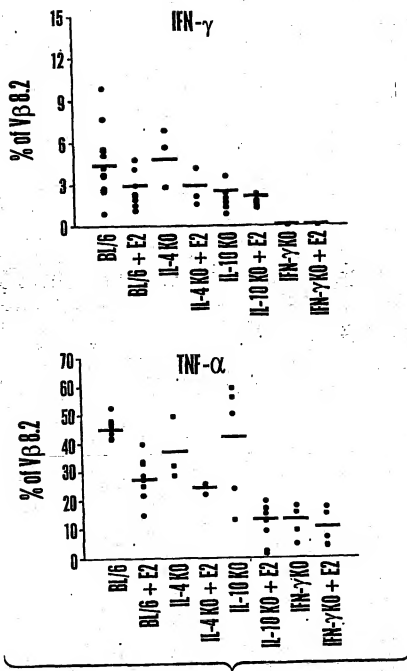


Figure 21C

The first part of the paper discusses the importance of the problem and the need for a systematic approach to its solution. It then presents a review of the existing literature on the topic, highlighting the strengths and weaknesses of various methods. The second part of the paper describes the proposed methodology, which is based on a combination of analytical and numerical techniques. The results of the study are presented in the third part, showing the effectiveness of the proposed method in solving the problem. Finally, the paper concludes with a discussion of the implications of the findings and suggestions for future research.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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International Bureau



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PCT

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**WO 01/085154 A3**

(51) International Patent Classification: **A61K 31/565**,  
A61P 37/00, 37/00 // (A61K 31/565, 38:10)

[US/AUS]; 8328 N.W. Ridgetop Court, Portland, OR 97229  
(US).

(21) International Application Number: PCT/US01/40710

(74) Agents: WEBSTER, Melanie, K. et al.; Campbell & Flores LLP, 7th Floor, 4370 La Jolla Village Drive, San Diego, CA 92122 (US).

(22) International Filing Date: 11 May 2001 (11.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 12 May 2000 (12.05.2000) US  
60/203,980

(63) Related by continuation (CON) or continuation-in-part  
(CIP) to earlier application: 60/203,980 (CIP)  
US 12 May 2000 (12.05.2000)  
Filed on

(81) Designated States (*national*): AE, AG, AL, AM, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ (utility model), DE (utility model), DK (utility model), DM, DZ, EE (utility model), ES, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(71) Applicants (*for all designated States except US*): OREGON HEALTH SCIENCES UNIVERSITY [US/US]; Office of Technology Management, 3181 Sam Jackson Park Road, L335, Portland, OR 97201-3098 (US). THE GOVERNMENT OF THE UNITED STATES OF AMERICA [US/US]; d.b.a. The Department of Veterans Affairs, 810 Vermont Avenue, N.W., Washington, DC 20420 (US).

Published:  
— with international search report

(88) Date of publication of the international search report:  
29 August 2002

*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(72) Inventor; and  
(75) Inventor/Applicant (*for US only*): OFFNER, Halina

(54) Title: METHOD OF TREATING IMMUNE PATHOLOGIES WITH LOW DOSE ESTROGEN

(57) Abstract: The invention provides a method of ameliorating a Th1-mediated immune pathology in a mammal. The method is practiced by administering a low dose of estrogen to the mammal. Optionally, an immunotherapeutic agent can also be administered to the mammal. Also provided are kits containing a low dose of estrogen and an immunotherapeutic agent.

WO 01/085154 A3

## INTERNATIONAL SEARCH REPORT

 Inter. Application No  
 PC/US 01/40710

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/565 A61P37/00 A61P37/00 //(A61K31/565, 38:10)

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)  
 IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

MEDLINE, EPO-Internal, PAJ, WPI Data, BIOSIS, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	OFFNER H. ET AL.: "Estrogen potentiates treatment with T-cell receptor protein of female mice with experimental encephalomyelitis." J. CLIN. INVEST., vol. 105, no. 10, 1 May 2000 (2000-05-01), pages 1465-1472, XP002189652 * see abstract, page 1465, page 1469 left col. and fig.3 *	1,2,4, 7-19,33
Y	---	1-20
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 1998-422294 XP002189653 & JP 10 175854 A (DOCTORS COSMETICS YG), 1998 abstract ---	1-3,6,7, 12,13
	---	

-/-

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"U" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"S" document member of the same patent family

Date of the actual completion of the international search

8 February 2002

Date of mailing of the international search report

Name and mailing address of the ISA

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 Fax: (+31-70) 340-3016

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Merckling, V

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# INTERNATIONAL SEARCH REPORT

Int. Application No.  
F01/05 01/40710

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		Relevant to claim No.
Category *	Citation of document, with indication, where appropriate, of the relevant passages	
X	PATENT ABSTRACTS OF JAPAN vol. 11, no. 0, 1998 & JP 10 175854 A (DOCTORS COSMETICS YG), 1998 abstract	1-3,6,7, 12,13
X	--- EP 0 159 739 A (AKZO NV) 30 October 1985 (1985-10-30) * see claim 1, page 3 and page 5 lines 12-22 *	1-4,12, 13
X,P	--- WO 01 32680 A (FRITZEMEIER KARL HEINRICH ;KOLLENKIRCHEN UWE (DE); BOLDOL WERNER ( ) 10 May 2001 (2001-05-10) * see abstract, claim 47 and pages 22-23 *	1-3
X	--- JANSSON L'ET AL: "Estrogen induces a potent suppression of experimental autoimmune encephalomyelitis and collagen-induced arthritis in mice." JOURNAL OF NEUROIMMUNOLOGY, (1994 SEP) 53 (2) 203-7. XP001012662	1,2,4, 7-13
Y	* see abstract, page 204 left col. last paragraph, page 205 left col., fig. 1 and 2 *	1-20
	-----	

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US 01/40710

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(e) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 1-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-15, 16 (part), 17-19, 20 (part), 33 (part)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.



FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

The person skilled in the art is not capable of determining unambiguously which diseases/conditions fall under the scope of the expression "Th1-mediated immune pathology" in claim 1. The search has been restricted to autoimmune diseases, as claimed in dependent claim 2. Present claims 1-6 and 9-33 relate to an extremely large number of possible estrogen compounds (see page 12 line 11 to page 13 line 7). Support within the meaning of Article 6 PCT and or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to steroidal compounds having an estrogenic activity, as defined on page 12 lines 11-27.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-15, 16 (part), 17-19, 20 (part), 33 (part)

Use of low dosage estrogen for the manufacture of a medicament for treating Th1-mediated diseases (autoimmune diseases). Use in combination with a T cell receptor peptide.

2. Claims: 16 (part), 20 (part), 33 (part)

Use of low dosage estrogen, in combination with a HLA peptide, for the manufacture of a medicament for treating Th1-mediated diseases (autoimmune diseases).

3. Claims: 16 (part), 20 (part), 33 (part)

Use of low dosage estrogen, in combination with an antigen peptide, for the manufacture of a medicament for treating Th1-mediated diseases (autoimmune diseases).

4. Claims: 21-32, 33 (part)

Use of low dosage estrogen, in combination with an immunoblocking agent such as an antibody, peptide ligand or cytokine, for the manufacture of a medicament for treating Th1-mediated diseases (autoimmune diseases).

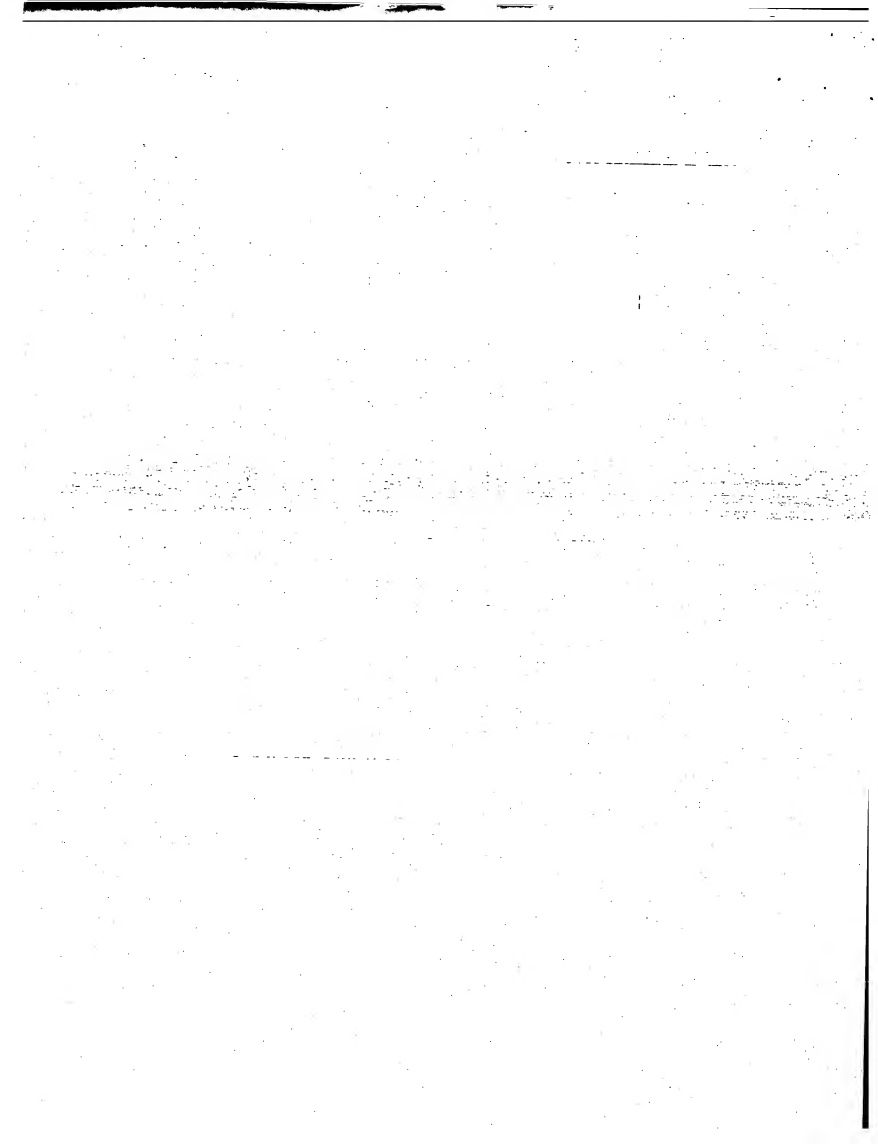
# INTERNATIONAL SEARCH REPORT

tion on patent family members

Interr Application No

PC1/US 01/40710

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 10175854	A	30-06-1998	NONE	
EP 0159739	A	30-10-1985	AT 42895 T DE 3570038 D1 EP 0159739 A1 JP 1829698 C JP 60209599 A MX 9203811 A1 US 4701450 A	15-05-1989 15-06-1989 30-10-1985 15-03-1994 22-10-1985 01-07-1992 20-10-1987
WO 0132680	A	10-05-2001	DE 19954105 A1 AU 1855201 A WO 0132680 A2	17-05-2001 14-05-2001 10-05-2001



CORRECTED VERSION

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15 November 2001 (15.11.2001)

PCT

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(51) International Patent Classification: A61K 31/565,  
A61P 37/00, 37/00 // (A61K 31/565, 38:10)

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(22) International Filing Date: 11 May 2001 (11.05.2001)

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(26) Publication Language: English

(30) Priority Data: 12 May 2000 (12.05.2000) US  
60/203,980

(63) Related by continuation (CON) or continuation-in-part  
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(54) Title: METHOD OF TREATING IMMUNE PATHOLOGIES WITH LOW DOSE ESTROGEN

(57) Abstract: The invention provides a method of ameliorating a Th1-mediated immune pathology in a mammal. The method is practiced by administering a low dose of estrogen to the mammal. Optionally, an immunotherapeutic agent can also be administered to the mammal. Also provided are kits containing a low dose of estrogen and an immunotherapeutic agent.

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